Canadian Association of Neuropathologists

Abstracts
of papers presented at
The 27th Annual Meeting
October 1987

Summary

The 27th Annual Meeting of the Canadian Association of Neuropathologists was held October 8th till 10th, 1987 at the Empress Hotel, Victoria, British Columbia. The meeting was attended by 84 members and guests. The scientific program consisted of 15 diagnostic case presentations, 17 other platform presentations, and 2 poster presentations.

Two guest lectures were presented to the meeting, namely:

The Royal College of Physicians and Surgeons of Canada Lecture

Dr. Stephen J. De Armond, Department of Pathology, School of Medicine, University of California, San Francisco

Title: "Novel Mechanisms of C.N.S. Degeneration: The Prion Hypothesis"

The Jerzy Olszewski Guest Lecture

Dr. Donald W. Paty, Division of Neurology, University of British Columbia, Vancouver, B.C.

Title: "The Use of Magnetic Resonance in the Evaluation and Follow-up of Inflammatory and Demyelinating Diseases of the Central Nervous System"

Two awards for presentations by trainees were given:

The Mary Tom Award: Dr. Emma Lew, Saskatoon, Saskatchewan: "A New Type of Neuronal Inclusion in Human Pathology."

The Morrison H. Finlayson Award: Dr. Frank Denardi, Ottawa, Ontario: "The Incidence of Amyloid Deposits in Pituitary Adenomas: A Review of 31 Cases."

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Abstracts

1.

The Large Anterior Horn Cells in Normal and in ALS Spinal Cords as Revealed by the Golgi-Cox Method

A. HIRANO and T. KATO (Bronx, N.Y., U.S.A.)

Many aspects of the morphology of the human anterior horn cell in both normal individuals and in ALS patients are still unknown. We have applied the Golgi-Cox method to transverse sections of lumbar cords in the normal cord and in ALS. Anterior horn cells in normal lumbar cords fell into 3 fairly distinct groups. They were biopolar, tripolar or multipolar shaped. Axons showed the expected morphology with tapering axon hillocks and initial segments with an enlargement at the first myelinated segment. The axon usually arose from the soma but sometimes from the proximal portion of a dendrite. In ALS, various abormal changes were found in anterior horn cells. In some the axons did not assume a larger caliber after narrowing in the initial segment. The dendritic tree was sometimes poorly developed and the dendrites were thin. Some cell processes with focal swellings were observed. So far as we know, this is the first report of a Golgi-Cox study of ALS spinal cords. (Supported by NIH Grant #2P50 NS 11605-9.)

2.

Long Term Endoneurial Changes in the Distal Stump After Total Axotomy

M. RÖYTTÄ and V. SALONEN (Turku, Finland)

Previously, a reversible compartmentalization of the endoneurial space in the distal stump of the transected nerve of rat has been shown by us (Acta Neuropathol., in press). In this process, a newly synthesized thin, 25-30 nm collagen fibrils could be noted around bands of Buengner, often separated by noncollagenous space from regular 50-60 nm collagen fibrils. These became surrounded by long cytoplasmic extensions of endoneurial cells forming minifascicles. These formations diminished within 8 weeks with the advancing myelination of axonal sprouts but were well preserved in nerves the axonal sprouting has been prevented by suturing.

In the present, extended study the corresponding endoneurial changes were examined 8, 10, 16, 30 and 50 weeks post nerve transection. Distal stumps of both non-regenerating and regenerating nerves were studied.

In the sutured nerves the endoneurial compartments were clearly visible 20 weeks PI, although Schwann cell columns (SC) were shrunken. After 30 weeks the Schwann cell loss was obvious. The endoneurial cells lost their delicate cytoplasmic processes, became covered by discontinuous basal lamina and formed larger, "macrofascicle"-like structures. The areas previously occupied by endoneurial cell processes became filled with microfibrils of 10-12 nm in diameter. These fibrils surrounded the earlier compartments around a shrunken SC or areas, where Schwann cells were lost and replaced mainly by regular thick collagen fibrils. Additionally, an increasing number of large accumulations of microfibrils which seemed to originate from SC were seen after 30 weeks. After 50 weeks the morphological alterations were in focal areas similar to those noted in Renaut bodies. Despite suturing to prevent axonal sprouting, some excaped sprouts could be noted growing inside endoneurial cell fascicles and formed onion bulb-like structures. In reinnervating nerves a gradual organization towards normal appearing endoneurial space was noted.

The present results show that after nerve transection the endoneurial space is actively organized, possible to enhance the growth of axonal sprouts. The distal stumps chronically deprived from axons show a gradual organized type of degeneration which may have relevance to chronic pathologic processes in the peripheral nerve.

3.

Additional Pathological Features in Epileptic Patients Secondary to Brain Tumours

SHI TING HUI, SYLVIA GAYTAN-GARCIA and J.C.E. KAUFMANN (London, Ontario)

During a span of 13½ years (February 1974 to August 1987), 245 patients underwent unilateral corticectomy or lobectomy at the University Hospital to control drug-resistant seizures. Neuropathological examination showed primary brain tumours in 81 cases (33%) among these, gliomas had a notable preponderance over non gliomas (75:6). In general, the great majority of the tumours were of small size and in an early stage of growth; a a result, the changes in the background had not yet been obliterated by tumour growth. Apart from the morphological changes directly relating to the brain tumours there were abnormalities indicating disturbance of neuronal migration and maturation. Coexistence of glioma and cortical dysplasia may provide some evidence for a relationship between dysgenetic abnormalities and neoplasm and could be the morphological substrate in cases of brain gliomas associated with seizures. In addition the neuron density in the epileptogenic tumour was measured compared with the site and type matched controls; there seem to be significant differences between the two groups.

4.

A New Type of Neuronal Inclusion in Human Pathology

E.O. LEW, B. ROZDILSKY, D.G. MUNOZ and G. PERRY (Saskatoon, Saskatchewan and Cleveland, Ohio, U.S.A.)

A novel, previously unreported neuronal cytoplasmic inclusion is described in a case of presumed metabolic encephalopathy. This female infant was the second-born to non-consanguinous, phenotypically normal parents. From the age of two months, signs of a subacute neurological syndrome were evident characterized by spasticity, tremor, spitting up of feeds, and developmental delay. There was progressive neurological deterioration to a state of hypotonia, accompanied by inspiratory stridor, dysphagia and terminal aspiration at 13 months. Postmortem examination of the brain (700 grams) showed cortical thinning and ventricular dilatation. Microscopically, symmetrical lesions were identified in the region of the reticular formation in the medulla. These lesions depicted capillary proliferation, vacuolation of the neuropil,

and demyelination, with relative preservation of the neurons, a constellation of features compatible with that seen in Leigh's disease. Less florid changes were noted in the H3 sector of the hippocampus, the walls of the third ventricle, the periaqueductal grey matter, and the floor of the fourth ventricle. More intriguing was the universal finding of single, and frequently multiple, ovoid eosinophilic cytoplasmic inclusions in virtually every neuron throughout the brain and spinal cord. The inclusions were sharply delineated and measured up to 11 microns in diameter, but did not distend or distort the cell profile. They did not stain with the PAS, Alcian blue and Bielschowsky techniques. Ultrastructurally, the inclusions comprised non-membrane bound aggregates of randomly oriented structures, which initially appeared to be of two different kinds: electron-densed curvilinear filaments and lighter osmiophilic plates. Tilting revealed that the filamentous configurations represented an end-on view of the plates. These plate-like entitites presented a parallel grid pattern of linear densities with a periodicity of 11 to 16 nanometers. Immunoperoxidase technique revealed strongly positive staining with antitropomyosin, weakly positive staining with antiactins, and negative results with antibodies to neurofilaments, tau protein, paired helical filaments, vinculin, ubiquitin, α - actinin and tubulin. These inclusions, which we have called tropomyosin aggregates, are therefore both ultrastructurally and immunocytochemically distinct from Hirano bodies. The formation of the tropomyosin aggregates in neurons presumably resulted from the same metabolic defect which caused the Leigh's disease type lesions.

5.

Glial Cells as Substrate for Axonal Elongation In Vitro

D.G MUNOZ, T. HA and R. UITTI (Saskatoon, Saskatchewan)

During development, axons of CNS neurons extend in contact with glial cell surfaces. However, adult mammals show very limited regeneration of interrupted CNS tracts, although mature CNS neurons are capable of extending axons through favorable substrates, such as implanted bridges of peripheral nerve, or embryonal CNS. It has been proposed that mature astrocytes (Kalderon, 1986) or reactive astrocytes formed in response to injury (Reier et al, 1982) act as a barrier to axonal regeneration. Astrocytic cultures have been shown to provide an excellent substrate for axonal elongation of central and peripheral neurons (Fallon, 1985; Noble et al, 1984). We have investigated whether the capacity of astrocytes to sustain axonal growth is modified by aging in culture, or by the transformation induced by dibutyryl cyclic AMP (dBcAMP) considered by some (Federoff et al, 1984) a model of reactive astrocytosis. Glial monolayer cultures, consisting predominantly of flat astrocytes, were obtained from dissociated neopallia of newborn Swiss mice. Cells were plated at a density of 400/mm^2 on plastic tissue culture dishes and fed regularly with modified Eagle's MEM plus 10% fetal calf serum. From the 14th day in-vitro on, some cultures were continuously treated with 0.25 mM dBcAMP. Astrocytes responded by extending numerous processes and markedly increasing GFAP immunofluorescence. Retinal fragments obtained from embryonic day 13 mice were explanted on top of cultures aged 1 - 6 weeks, and 48 hours later the cultures were fixed and stained with a monoclonal antibody directed against phosphorylated neurofilaments. The explants extended profuse neurites in a radial pattern on the surface of the astrocytes. The length of the neuritic halo was compared by analysis of variance between cultures of different ages, and between treated and untreated cultures. No significant differences were found. Dorsal root ganglia explants also grew equally well on treated and untreated cultures. Aging in culture, or the changes induced by dBcAMP do not affect the capacity of astrocytes to act as a substrate for the growth of immature axons.

6.

A Peroxisomal Disorder of Infancy Mimicking Cerebrohepatorenal Syndrome of Zellweger

E.S. JOHNSON and P. FERREIRA (Edmonton, Alberta)

The cerebrohepatorenal syndrome (CHRS) of Zellweger is characterized by an absence of peroxisomes and aberrant metabolism of very long chain saturated fatty acids and plasmalogens. In this case report we describe a one-year-old girl whose clinical presentation at birth closely resembled CHRS with characteristic facial dysmorphism, profound hypotonia, and onset of generalized and myoclonic seizures. Analysis of plasma and fibroblast cultures revealed marked accumulation of C_{26} fatty acids. However, peroxisomal synthesis of plasmalogens in fibroblast cultures was preserved. The clinical course, furthermore, differed in being more prolonged and unassociated with any biochemical disturbances in liver function. At autopsy neuropathological abnormalities similar to those described in CHRS are found: dysplasia of the inferior olivary nucleus, cerebellar neuronal heterotopias, focal cerebral polymicrogyria, and bilateral subependymal cysts. Marked demyelination with florid gliosis is present in the cerebral and cerebellar white matter. Superimposed, however, is widespread ischemic necrosis causing hemiatrophy of the right cerebral hemisphere. Unlike CHRS there are no renal cysts nor is there hepatic fibrosis, and electron microscopy reveals the presence of large peroxisomes with dense inclusions in the liver. In addition, there is severe atrophy of the adrenal cortex with the remaining adrenocortical cells containing cytoplasmic lamellar inclusions similar in ultrastructure to the inclusions noted in the CHRS, neonatal adrenoleukodystrophy and other peroxisomal disorders. Lamellar inclusions are also noted in Schwann cells in the posterior tibial nerve, in which there is a demyelinating neuropathy with early interstitial hypertrophic change. The observations in this case, and a recently reported similar case, suggests the existence of disorders which closely mimic CHRS and share common ultrastructural and biochemical features, but differ in the pathogenesis of the peroxisomal metabolic defect.

The authors wish to gratefully acknowledge the assistance of Dr. Ann Moser, Johns Hopkins University School of Medicine, for the biochemical analyses and Dr. M. Beard, Columbia University, for electron microscopic cytohistochemistry studies.

7.

Correlations Between Alkaline Phosphatase Activity and Exchange Functions of Brain Microvasculature

M.A. BELL, D.M. MOODY, J.N. ANGELO, V.R. CHALLA and T.C. JOHNSTON (Winston-Salem, North Carolina, U.S.A.)

Alkaline phosphatase activity in cell membranes probably signals the active transport of some substance either completely across the cell, or at least into or out of the cell across the membrane concerned. Well known examples include the brush borders of the epithelial cells of the kidney proximal tubule and the gut lining. Several but not all vascular systems exhibit phosphatase staining in the endothelium of the small exchanging vessels, the chief and most exploited example being the CNS microvasculature.

In the human brain, large arteries do not stain, arterioles and capillaries do, and the transition from non-staining to staining regions may display a curious streaky pattern. Venules do not stain, but a few veins in periventricular locations do. The apparent equation between phosphatase staining and exchanging function in small vessels is further reinforced by the similar distribution of Pfeiffer's cylinder, the avascular column of parenchyma that rings the stained arterioles, implying that they have a role in nourishing their surroundings and are not merely adjustable conduits.

The putative correspondence between phosphatase staining and vascular exchange functions in the brain raises interesting points in relation to arteriole-venule pairs, stained periventricular veins, the membrane localization of endothelial activity, and particularly the vexed question of the staining characteristics of barrier vessels versus leaky ones. The

choroid plexus and area postrema vessels provide striking examples and an ample base for discussion of the latter point.

Our material does not support the thesis that alkaline phosphatase activity corresponds to the presence of a tight vascular barrier. We submit rather that it is associated more generally with the exchanging portions of the microvascular bed, but even this cautious view encounters inconsistencies.

8.

An Autopsy Case of Congential Neuro-syphilis

SHUNJI MAEKURA, TOMOHIRO YAMADA and SHIGEO HASHIMOTO (Osaka, Japan)

Six-month-old male infant, whose mother was diagnosed as having syphilis at 7 months of pregnancy. The infant was delivered prematurely at 30 weeks. The birth weight was 1537 g. Apgar score 8. IgM-FTA-ABS was positive in the umbilical blood. He was treated with penicillin for ten days. During the first three days after birth, he suffered from episodes of anoxia. One month later, he suffered from convulsive seizures and was treated with anticonvulsant without success. Six months later, he died of pneumonia accompanied by pulmonary hemorrhage. At autopsy, the brain (580 g) showed significant cortical atrophy, the right hemisphere being smaller than the left. There was diffuse clouding and thickening of the leptomeninges especially in the occipital area, where there was moderate hydrocephalus. The border between cerebral cortex and white matter was indistinct. The cerebral cortex was slightly firmer especially in the occipital area, and the white matter showed diffuse increase in consistency.

Light microscopic examination of the brain revealed marked, but irregular gliosis of the cerebral cortex and, to a lesser extent, of the subcortical white matter. One of the most striking findings of this case was hypertrophy of small cortical arteries. Some blood vessels showed marked tortuosity. Inflammatory reactions, perivascular or elsewhere, were limited. Scattered calcific spherules were noted in the cortex and some of the white matter blood vessels were heavily calcified.

9.

Focal Nodular Glial Differentiation in Choroid Plexus Hemangioma

KHANG-LOON HO (Detroit, Michigan, U.S.A.)

Normal choroid plexus epithelium shows no immunoreactivity for GFAP. However, in choroid plexus papillomas and carcinomas focal positivity for GFAP has been observed in as many as 40% of these tumours. The presence of GFAP positive cells has been interpreted as an indication of glial and presumably ependymal differentiation related to neoplastic transformation of the choroid plexus epithelium. Such glial differentiation is in keeping with the ontogenetic derivation of the choroid plexus epithelium from the primitive neuroepithelial cells. *Glial differentiation of the choroid plexus epithelium has not been* described in pathologically altered conditions other than neoplasms. This report describes an unruptured hemangioma (vascular malformation) located in the distal half of the choroid plexus of the lateral ventricle in a premature stillborn baby. Along the flattened choroid plexus epithelium covering the hemangioma there were scattered neuroglial nodules which stained strongly for GFAP. GFAP positive cells were not present elsewhere in the choroid plexus. The topographic distribution, morphological configuration and cellular composition of the neuroglial nodules were closely similar to that of ependymal nodules (ependymal granulations) in the ventricular surface. The neuroglial nodules were confined within the basement membrane of the choroid plexus epithelium. It is unlikely that the neuroglial nodules resulted from proliferation of subjacent stromal cells with subsequent uptake of GFAP. The neuroglial nodules are interpreted as nodular proliferation of reactive choroid plexus epithelial cells with glial divergent differentiation. While the reactive capacity of the choroid plexus epithelium has generally been regarded as limited or even non-existent, the present study demonstrates that in certain pathological conditions the choroid plexus epithelial cells may express proliferative activity in the form of neuroglial nodules. The mechanism of such unusual reactive proliferation and glial differentiation of the choroid plexus epithelium is unknown.

10.

Heinsenberg's Uncertainty Principle as Related to the Diagnosis and Treatment of Cancer

ELLSWORTH C. ALVORD, JR. (Seattle, Washington, U.S.A.)

Heisenberg's uncertainty principle was originally developed at the level of subatomic physics: "We cannot know both the position and the momentum of a particle with absolute precision" and ". . . we cannot observe something without changing it." As applied to the diagnosis of cancer, a "position" (histologic appearance) is observed and a "momentum" (prognosis or rate of growth) predicted. With the development of improving methods of diagnosing cancers an additional element has entered in which the new "position", previously unknowable by older diagnostic techniques, is being used to define a treatment that is hoped will decrease the "momentum". Not only was the old "momentum" poorly defined, since growth rates and histologic appearances show broadly overlapping rather than discrete correlations, but also the new "momentum" from the new "position" is not derivable from the old data and is, therefore, unknowable at the present.

The logical approach to resolving this absurd state of affairs would be to define the growth rate for each tumour before treatment is begun. An alternate approach would be to define the growth rates for better-defined histologic subgroups of tumours. A third approach is to try to define the natural history of certain neoplasms, to see which ones follow some reasonable pattern.

The simplest hypothesis concerning rates of growth of cancers is an exponential one, the volume-doubling time being constant. During the past decade we have used Collins' extension of this hypothesis to examine the natural history of ependymomas, cerebellar astrocytomas, optic gliomas and meningiomas. Ependymomas appear to have growth rates that correlate with the patient's age, whereas the other two gliomas have such a broad range of growth rates that none can be predicted in any particular case. Optic gliomas often appear to slow down after diagnosis. So far, only meningiomas appear to have growth rates that correlate with the histologic appearances but even here only the extremes (grades 1 and 3) show little overlap. Epidermoid tumours, like skin with a single layer of dividing basal cells, grow linearly, rather than exponentially.

11.

Amyloid Gene Expression is Decreased in Alzheimer Disease

A.W. CLARK, C.A. KREKOSKI, I.M. PARHAD, D. LISTON, D.I. HOAR and J.-P. JULIEN (Calgary, Alberta and Montreal, Quebec)

In Alzheimer disease (AD) amyloid accumulates in blood vessels and neuritic plaques. This polypeptide is a cleavage product of a larger precursor protein whose gene has been localized to chromosome 21 and is preferentially expressed by large neurons in cortical layers III and V, cells which are particularly susceptible to degeneration in AD. We evaluated mRNA expression of the amyloid precursor in parietal cortex of 6 cases of AD and 6 age-matched controls. Postmortem intervals for the two groups were similar (AD, 8.2 ± 2.9; controls, 9.8 ± 2.6 hours). AD-type degeneration and amyloid accumulation were

severe in the AD cases, and absent or minimal in controls. A cDNA library was prepared from adult human, AD-affected brain. The library was screened using a synthetic oligonucleotide based on the previously published amino acid sequence for the amyloid in AD (Masters et al, Proc Natl Acad Sci USA 1985). The cNDA selected was characterized by restriction endonuclease mapping and found to correspond to that subsequently reported by Kang et al (Nature 1987). From this cDNA, a 240 bp Hinc II fragment encompassing the coding region for the amyloid polypeptide was radiolabeled and used to probe Northern transfers of total RNA. For comparison, cDNA probes for three cytoskeletal proteins were used to probe the same material: the human 68 kD neurofilament subunit (NFL) (Julien et al, Biochim et Biophys Acta 1987), α-tubulin (Lewis et al, J Cell Biol 1985), and glial fibrillary acidic protein (GFAP) (Lewis et al, Proc Natl Acad Sci USA 1984). One-dimensional scanning densitometry showed a marked decrease in expression of the amyloid precursor in AD cortex as compared to controls. Expression of α-tubulin and NFL were also significantly decreased in AD cortex while expression of GFAP was slightly increased. The methods employed in this study detected differences in cytoskeletal protein mRNA expression which were not detected in earlier studies using cytoplasmic dot hybridization. These results indicate a selective decrease in expression of certain mRNAs, including that for the amyloid precursor, in AD. This is consistent with relative preservation of glial mRNAs, with simultaneous loss of mRNAs from vulnerable neuronal subsets in AD.

12.

Post Ischemic Hypoglycemia Reduces Ischemic Damage to Cerebral Cortex and Hippocampus in the Rat

R.N. AUER and C.L. VOLL (Calgary, Alberta)

The possible therapeutic value of lowering post-ischemic blood glucose levels in stroke was investigated in a rat model of transient forebrain ischemia. Moderate pre-ischemic glucose loading, known to produce infarction, was given to each of 3 groups. Following 10½ min of cerebral ischemia induced by carotid clamping and hypotension, either no treatment (control; blood glucose levels 12-15 mM), low dose insulin (2-3 IU/kg - blood glucose levels 2-5 mM), or high dose insulin (8-20 IU/kg - blood glucose levels 1.2-3.5 mM) regimens were given.

The effects of low and high dose insulin were different, both clinically and neuropathologically. Survival was improved over controls by low dose insulin, and post-ischemic epilepsy was alleviated. In contrast, high dose insulin aggravated post-ischemic epilepsy, and thereby increased seizure-related mortality over controls.

Quantitative neuropathologic assessment showed no improvement in selective neuronal necrosis in the low dose insulin group. However, cortical infarcts were not seen in the low dose insulin group whereas the control group showed cortical infarcts in 50% of the animals. High dose insulin also prevented cortical infarcts, and in addition produced a pronounced reduction in selective neuronal necrosis in the cerebral cortex and hippocampus compared to controls receiving no post-ischemic insulin. However, brain stem damage related to post-ischemic audiogenic running seizures was seen in the substantia nigra, pars reticulata and in the inferior colliculus of the high dose insulin animals.

The findings suggest that post-ischemic insulin administration may be useful in reducing brain necrosis after transient cerebral ischemia. However, careful monitoring of blood glucose levels and vigilance for an increase in the normally low rate of post-ischemic epilepsy in the human will be required for future application of this treatment in man.

13.

Does Chronic Alcohol Intoxication with a Vitamin A Deficient Diet Potentiate the Formation of Paired Helical Filaments (PHF) in Dorsal Root Ganglia (DRG) of Rats?

S. DANCEA, V.J.A. MONTPETIT, S.W. FRENCH and D.F. CLAPIN (Ottawa, Ontario)

The lack of a suitable animal model for Alzheimer research has been a continuing impediment to the elucidation of the pathogenesis of this disease. However, PHF-like filaments occur spontaneously in DRG of aged rats (van den Bosch de Aguilar, 1984) and chronic ethanol intoxication induces the formation of PHF in younger rats (Volk, 1980). We present evidence that a vitamin A deficient diet promotes the formation of PHF in DRG of rats chronically intoxicated with ethanol.

Three groups of young male Wistar rats weighing 350 to 400 g were implanted with a single gastrostomy cannula and infused with the following liquid diets: first group received 30% of total calories as corn oil, 32% as ethanol, 25% as protein with the balance as dextrose; 5% lard was substituted for the corn oil in second group; the third group received 25% corn oil and was maintained in a vitamin A deficient state. Control animals were isocaloric in dextrose with the experimental animals' alcohol intake. Animals were sacrificed at approximately 150 days and DRG were fixed in situ with a solution containing 2% paraformaldehyde and 2% glutaraldehyde.

An increased number of nematosomes was noted in all ethanol treated rats, most striking in animals with a vitamin A deficient diet. Large amounts of lipofuscin was usually associated with these thread-like structures which were of several types (Montpetit et al, 1987). Nematosomes commonly enclosed neurofibrillary tangles of PHF in animals treated with ethanol vitamin A deficient diet. PHF were rarely observed in other animals. PHF consisted of pairs of filaments with a diameter of 8-10 nm, having a double helix diameter of 16-24 nm with a periodicity of 30-38 nm. Their close association with polyribosomes as described in Alzheimer's disease was also noted (Metuzals et al, 1981). Focal accumulations of densely packed 11-12 nm neurofilaments were seen in proximal myelinated axons of all rats.

We conclude that the cytoskeletal pathology produced in alcohol intoxicated rats, namely the PHF, is similar to the neuronal alterations noted in human conditions such as Alzheimer's disease. We also conclude that the vitamin A deficient diet may promote the formation of PHF.

14.

Gene Expression of Cytoskeletal Components in Aluminum Myelopathy

I.M. PARHAD, C.A. KREKOSKI and A. MATHEW (Calgary, Alberta)

Aluminum (Al) salts when given intracisternally to weanling rabbits produce a myelopathy which consists of neurofilament (Nf) accumulation in neuronal cell bodies and proximal axons. Pathogenetic studies have shown a delay in the exit of Nf proteins from the cell body, as well as an ectopic phosphorylation of a Nf component. In this study we looked at the role of gene expression of Nf proteins as well as other cytoskeletal components in the pathogenesis of this model. Three week old albino rabbits were given an intracisternal dose of $AlCl_3$ (1% solution, 100-200 μl, pH 3.4) and killed 2, and 7 days later; each rabbit had an age matched control which was given an intracisternal dose of saline (pH 3.4). Spinal cords were evaluated neuropathologically and total RNA was quantitated. Northern transfers were prepared using total RNA and the blots were hybridized with radiolabelled cDNA probes. The following probes were used: Nf-L (Lewis & Cowan, 1985) and Nf-M (Julien et al, 1986) for the 68 and 145 Kd Nf proteins, αl-tubulin (Lewis et al, 1985), α-actin (Minty et al, 1981) and GFAP (Lewis et al, 1984). Our results show that all the intoxicated animals had pathological lesions consisting of Nf accumulation in neurons at 2 and 7 days. The total RNA quantitated spectrophotometrically did not vary with age or with intoxication (2-ANOVA, $p>0.05$). One dimensional scanning densitometry of Northern blots showed a decrease in signal for the Nf probes and no significant alteration for the other cytoskeletal probes at 2 days. At 7 days the decrease in signal for the Nf probes was no longer apparent. We interpret our results to mean that Al has a selective and early effect on Nf gene expression.

15.

Iatrogenic and Spontaneous Aneurysms in a Case of Fibromuscular Dysplasia (FMD)

D. IZUKAWA, V.J.A. MONTPETIT, M. RICHARD, M. RIDING, M. LAURIN and R. NELSON (Ottawa, Ontario)

FMD is a segmental, non-atheromatous and non-inflammatory disorder of muscular arteries characterized by irregular fibrous or fibromuscular thickening of the intima, media or adventitia. The classic angiographic "string of beads" pattern and the topography of the lesions are considered pathognomonic of the disease in the cephalic arteries. However, pathologic verification of the lesions is available in a small percentage of cases. FMD of the cervical arteries is often associated with intracranial aneurysms, most commonly located on the same side as the affected vessel, suggesting that the aneurysms and the FMD are related. Histologic documentation of this association has been reported only in a few cases.

A 36-year-old woman was admitted with sudden onset of severe left-sided headache and neck pain which had been intermittent for approximately one week. Examination revealed a distressed lady holding the left side of her head and with definite neck stiffness. Cerebral angiographic studies using a five French Mani catheter disclosed a corrugated right vertebral artery at the level of C 2 and areas of narrowing in the right internal carotid. The extra and intracranial portions of the left internal carotid artery, as well as the proximal middle cerebral artery were significantly larger than normal and displayed segmental constrictions. Subintimal contrast material was noted 4 cm distal to the origin of the internal carotid together with a 4 mm aneurysm 7 mm from the bifurcation and therefore distal to the ophthalmic. The patient died suddenly three days after an uneventful surgical clipping of the aneurysm. The autopsy showed multifocal vascular anomalies characterized by intimal and medial fibroplasia most pronounced in the left internal carotid artery. The dissecting aneurysm extended to the base of the cranium and the ruptured aneurysm originated from an ectatically dilated internal carotid artery.

The etiology of FMD is unknown. Since 90% of cases are found in females, an endocrine cause has been proposed by some investigators. Others have favoured a response to trauma as a more plausible etiology since FMD is commonly found in arteries subject to mechanical stretching such as the cervical, mesenteric and renal arteries. Mettinger et al study suggests that FMD is a congenital mesenchymal disorder. It is noteworthy that our patient's mother had an inoperable cranial aneurysm. Experimental work support an ischemic theory based on absence or diminution of vasa vasorum. The cause of this disease process is probably multifactorial.

16.

Perineurioma, Fibrolipoma of Median Nerve, and Macrodystrophia Lipomatosa: Separate and Distinct Entities or a Pathologic Spectrum?

S.C. BAUSERMAN, T.Y. SCHWEITZER and J.C. STINSON (Temple, Texas, U.S.A.)

Perineurioma (Localized Hypertrophic Neuropathy) is a fusiform swelling of a peripheral nerve composed of concentric whorls of perineurial cells and interspaced collagen surrounding myelinated, demyelinated, or remyelinated axons. It usually presents with motor and sensory abnormalities, not generally as a mass, and has been described in the posterior interosseous, radial, median, tibial, popliteal, and axillary nerves, and the lateral cord of the brachial plexus.

Fibrolipoma of the median nerve is primarily fatty proliferation, either ensheathed in the epineurium or diffuse, with variable amounts of dense fibrous connective tissue. It commonly presents as a mass in the palm of the hand. Symptoms are usually those of compression within the carpal tunnel. Six of twenty cases found in the literature mention, in addition to the fatty proliferation, enlarged nerve bundles, some with encreased epineurial, perineurial, and/or endoneurial connective tissue. Published photographs from some of these cases reveal distinct whorl formations, virtually indistinguishable from the whorls found in perineurioma.

A third entity with overlapping clinical features is Macrodystrophia lipomatosa, a digital enlargement with localized overgrowth of bone and increased subcutaneous fat. Fibrofatty enlargement of the median and involved digital nerve is sometimes an additional component, with features histologically similar to fibrolipoma of the median nerve and perineurioma.

We present two cases from our recent and remote material which serve to illustrate some of these overlapping features. Case #1 was a 10-year-old male in 1957 who presented with painful paresthesias in a hypertrophied right ring finger, and a mass present in the palm. The digit was amputated and the palm surgically explored. Case #2 is a 21-year-old male who recently presented with a mass in the left index finger. A soft tissue resection of the mass was performed. The histologic, ultrastructural, and immunohistochemical features of this latter case are quite consistent with Perineurioma or focal hypertrophic neuropathy as described in previous literature. We conclude that there is significant overlap in these entities and suggest that a morphologic spectrum may exist between them.

17.

The Incidence of Amyloid Deposits in Pituitary Adenomas: A Review of 31 Cases

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Immunamyloid is well characterized. Amyloid of endocrine origin (apudamyloid), presumed to be derived from peptide hormones, is less well defined. It is noted regularly in medullary carcinoma and pancreatic islet cell tumour, but occurs less frequently in pituitary adenoma. Since the first report of amyloid bodies in a pituitary adenoma by Gartner in 1925, the number of case reports in the literature has been increasing. There have been only four studies which have attempted to determine the incidence of amyloid in pituitary adenomas; Pearse et al found none; Robert described 4 out of 214 cases (2%); Westermark et al reported 5 out of 21 cases (24%); and Saitoh et al reported 34 out of 48 cases (71%). This discrepancy in the frequency of amyloid accumulations prompted us to review the 31 cases of pituitary adenoma encountered at the Ottawa General Hospital since 1969. Seventeen adenomas occurred in males and 14 in females ranging in age from 19 to 66 years. Based on their histological, immunocytochemical and ultrastructural features, the adenomas were classified according to the method proposed by Horvath and Kovacs in 1986. There were 3 growth hormone cell, 8 prolactin cell (PRO), 2 mixed growth hormone-prolactin cell, 1 acidophil stem cell, 1 corticotroph cell, 7 gonadotroph cell, 3 null cell, 1 thyrotroph cell and 5 plurihormonal cell adenomas. For amyloid detection, Congo red and sulfated alcian blue stains were used. One of the 31 cases (3.2%) was found to have amyloid accumulating as spheroid bodies and was of the plurihormonal secreting cell type. Immunohistological stains for luteinizing hormone (LH), follicle stimulating hormone (FSH) and PRO were positive in tumour cells and within the amyloid bodies. PRL, FSH and LH secreting cells were confirmed ultrastructurally. Present in the extracellular space were large aggregates of radially oriented fibrillar material. Fibrils 9-12 nm in diameter formed small compact bundles intermingled with granular material. In areas where large amyloid bodies were surrounded by neoplastic cells, bundles of fibrils appeared to be released from these cells. Amyloid-like fibrils were noted in cytoplasmic vacuoles of the adenoma cells remote from the amyloid spherules. In summary, we have found that the frequency of amyloid accumulation in pituitary adenoma is rare and comparable to other series reported with one exception. Ultrastructural findings sup-

port the view that the amyloid is derived from the adenoma cells. The immunoreactivity of the amyloid bodies with PRO, LH and FSH suggest that the amyloid is hormonally derived. Analysis of the amino acid sequence of the amyloid and comparison of the results to the sequence of the hormone would clarify the origin of the amyloid. To our knowledge this is the first case of amyloid accumulating in a multihormone producing pituitary adenoma.

18.

Trans-synaptic Spread of Varicella Zoster Infection Through the Visual System in a Patient with AIDS

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The spectrum of central nervous system (CNS) infection by varicella-zoster virus (VZV) includes hematogenous dissemination, ascending sensory nerve infection, and angiitis. We report a patient with anatomic evidence of anterograde spread of VZV through the visual system. A 29-year-old homosexual male developed Acquired Immunodeficiency Syndrome (AIDS) 2 months prior to the onset of a zoster infection involving the ophthalmic branch of the left trigeminal nerve. During the next 10 months his zoster infection progressed to involve his left eye with resultant keratitis, iritis, retinitis, and eventual blindness. Later he reported loss of vision in the right eye which was thought to represent a post-chiasmal lesion. One year after the onset of his VZV infection he became bilaterally blind and hemiparetic on the left. He died of *Pneumocystis carinii* pneumonia. At autopsy the brain revealed destruction of the visual system and adjacent structures with sparing of the remainder of the brain. The left retina revealed extensive scarring and destruction but no evidence of active viral infection. The optic chiasm and both lateral geniculate bodies were largely destroyed by necrosis. Multiple areas of patchy necrosis were noted in the left calcarine cortex. Glial cells near the areas of necrosis showed Cowdry-A type intranuclear inclusions. In-situ hybridization with probes to VZV DNA were positive. Electron microscopy revealed characteristic herpes-type intranuclear virions. This is the first report to our knowledge of a trans-synaptic spread of VZV through the visual system and provides an additional mechanism for viral encephalitis in the immunocompromized host.

19.

Long-term Follow-up of Children with Ependymomas

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We reviewed 47 consecutive cases of Seattle-treated childhood ependymomas from our files between 1953 and 1985. Tumour locations were as follows: fourth ventricle, 35; lateral ventricles, 8; cauda equina, 4. Forty-one survived beyond surgery and had follow-ups ranging between 2 and 21 years (mean: 13.3 years). Histology correlated poorly with outcome with the following survival rates: low grade, 12/32; intermediate, 1/3; high, 1/5; mixed (low and high) 0/1. Prognosis was better related to the site of the neoplasm: 27% (8/30) of patients survived with tumour in the fourth ventricle, 37.5% (3/8) with tumour in the lateral ventricles, and 100% with tumours in the cauda equina (3/3). The latter most likely reflects the biology of the tumours characteristic for their location, i.e., low-grade myxopapillary ependymomas in the cauda equina are relatively radio-sensitive and have a good outcome. Tumours of the lateral ventricles were more likely to be high grade (5/8) than those from the fourth ventricle (no high grade, 1 mixed high and low grade, 2 intermediate grade out of 30 total) or cauda equina (0/3). One patient with a posterior fossa low grade ependymoma treated with surgery, chemo- and radiation therapy showed ependymoblastoma at autopsy. Therapies included the following: surgery followed by radiation and chemotherapy (survival: 4/8 patients), surgery followed by radiation alone (survival: 9/31 patiens), surgery alone (survival 1/2). Unfortunately autopsy rates dropped from 65% before 1975 to 20% since. Autopsy follow-up in 13 patients revaled local recurrence in all and no distant spread of the 7 low-grade tumours (spinal cord available in 4 of them). In contrast, 4 of the mixed or high grade tumours extended into the leptomeninges of the upper cervical cord and/or brainstem (2 cases), 1 extended down to the lower cervical cord, and 1 disseminated widely. Fourteen were alive without clinical evidence of disease (mean follow-up: 9.7 years). Eight of these survivors were at or beyond the threshold period of "risk" as defined by Collins' "law" (mean follow-up: 14 years; mean symptom-free ratio: 1.9). Two children died beyond the threshold of "risk" but had severe mental and neurologic handicaps which would have lessened the chance of detecting symptomatic recurrence. These studies add further evidence that ependymomas "obey" Collins' "law", and that control of the local disease with maximal surgical debulking followed by adjuvant radiation (and chemotherapy?) is important for prognosis.

TITLES OF DIAGNOSTIC CASE PRESENTATIONS

1. **Myotubular Myopathy. X-linked Lethal Neonatal Form.**
   M.G. NORMAN (Vancouver, British Columbia)
2. **Melanotic Medulloblastoma.**
   C.L. DOLMAN (Vancouver, British Columbia)
3. **Stretch Injury of Horizontal Axons of Medulla, a Consequence of Acute Downward Displacement, Shortening and Widening of Medulla from a Supratentorial Mass.**
   J.N. DECK (Toronto, Ontario)
4. **Glioblastoma Multiforme in a Patient with 18-Q Deletion, and Neurofibrillary Tangles in a Patient with 18-Q Deletion.**
   W.C. HALLIDAY (Winnipeg, Manitoba)
5. **Giant Cell Polymyositis and Myocarditis.**
   H.J. MANZ, J.C. KATTAH and L.E. ZIMMERMAN (Washington, D.C., U.S.A.)
6. **Vacuolar Myelopathy of A.I.D.S.**
   J. SHER (Brooklyn, New York, U.S.A.)
7. **Langerhans Cell Histiocytosis with Involvement of the Cerebellum.**
   D.P. AGAMANOLIS, C.E. KRILL and K.F. SWANSON (Akron, Ohio, U.S.A.)
8. **Axonal Depletion and Nonamyloid Deposits in IgM Neuropathy.**
   V. JAGADHA, J.M. BILBAO and C.A. SAWKA (Toronto, Ontario)
9. **Chordoid Meningioma.**
   I.R.A. MacKENZIE and J.C.E. KAUFMANN (London, Ontario)
10. **Iatrogenic Embolic Encephalopathy.**
    P.B. LITTLE, H. STAEMPFLI and D.P. KEANE (Guelph, Ontario)
11. **Neuromyelitis Optica (Devic's Disease).**
    L.C. ANG, J.J. GILBERT and P. COOPER (London, Ontario)
12. **Infantile Supratentorial Primitive Neuroepithelial Tumour with Glial and Neuronal Differentiation (Glioneuroblastoma).**
    J.B. LAMARCHE (Sherbrooke, Quebec)
13. **Myxopapillary Ependymoma Left Frontal Lobe.**
    J.B. SCHNITTKER, I. JADUSINGH and B. CURRIE (Calgary, Alberta)
14. **Subependymoma (Subependymal Glomerate Glioma) with Recent and Remote Hemorrhage and Degenerative Changes, Third Ventricle.**
    S.C. BAUSERMAN (Temple, Texas, U.S.A.)
15. **Granulomatous Angiitis of Spinal Cord and Brain Stem.**
    C.-M. SHAW (Seattle, Washington, U.S.A.)